(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 March 2002 (21.03.2002)

PCT

(10) International Publication Number
WO 02/22125 A1

(51) International Patent Classification[7]: A61K 31/47, A61P 31/22

(21) International Application Number: PCT/US01/28764

(22) International Filing Date:
11 September 2001 (11.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/240,946	15 September 2000 (15.09.2000)	US
09/932,479	17 August 2001 (17.08.2001)	US

(71) Applicant: **3M INNOVATIVE PROPERTIES COMPANY** [US/US]; 3M Center, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(72) Inventor: **SMITH, Michael, H.**; Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(74) Agents: **HOWARD, MarySusan** et al.; Office of Intellectual Property Counsel, P.O. Box 33427, Saint Paul, MN 55133-3427 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EC, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/22125 A1

(54) Title: METHODS FOR DELAYING RECURRENCE OF HERPES VIRUS SYMPTOMS

(57) Abstract: Novel dosing regimens of resiquimod formulations are disclosed for delaying recurrence of herpetic lesions in patients affected with a herpes virus infection. Preferably, dosing regimens include administering a pharmaceutical formulation containing resiquimod to a herpetic lesion once a week for at least one week.

METHODS FOR DELAYING RECURRENCE OF HERPES VIRUS SYMPTOMS

Field of the Invention

The invention is directed to novel dosing regimens for the administration of resiquimod. In some embodiments, the invention is particularly advantageous for delaying recurrence of symptoms associated with infection by double-stranded DNA viruses such as herpes simplex virus types 1 (HSV-1) and 2 (HSV-2).

Background of the Invention

Approximately 600,00 new cases of herpes simplex virus are diagnosed annually in the United States. The total number of people infected in the United States is estimated to be more than 40 million.

Herpes simplex virus is composed of a double-stranded DNA nucleoprotein core surrounded by an icosahedral protein capsid, which in turn is enclosed in a lipid and glycoprotein outer envelope. It is a member of a family of eight known related human herpes viruses, including herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV-6), human herpes virus 7 (HHV-7) and human herpes virus 8 (HHV-8). Many herpes viruses are capable of establishing latency in certain cell types, resulting in persistent infection.

Herpes simplex lesions can generally occur as a result of a primary (initial) infection or as a result of a recurrence (reactivation) at the same site. During acute primary infection, the herpes simplex virus may establish latent infection in the nerve root ganglia that corresponds to the cutaneous or mucous membrane site of inoculation. Herpes

simplex skin infections are usually located in the orolabial, genital or anorectal areas. Orolabial HSV infection is typically HSV-1 and genital is typically HSV-2; however, each site may be infected with the other HSV type. Following orolabial infection, HSV becomes latent in the trigeminal ganglia and after genital or anorectal infection, HSV becomes latent in the sacral ganglia. A variety of stimuli, such as ultraviolet light, fever, menstruation, stress, local skin trauma, or trauma to the sensory nerve, can reactivate latent HSV.

Most cases of HSV infection can be diagnosed by the morphological characteristics of the clinical symptoms including small, grouped vesicles on erythematous bases which then pustulate, ulcerate and later form a crust. Systemic symptoms can occur (e.g., fever, headache, myalgia, and malaise), but are more commonly associated with primary infection, especially genital herpes.

Resiquimod (4-amino-α,α-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol) is a member of the imidazoquinoline family of immune response modifiers. One member of this family, known as imiquimod, has been commercialized in a topical formulation, Aldara™, by 3M Company, St. Paul, MN, for the treatment of anogenital warts associated with human papillomavirus. Resiquimod has demonstrated potent antiviral activity in animal models. This activity appears to be mediated predominantly through the induction of cytokines, including interferon-α (IFN-α) and interleukin 12 (IL-12). Resiquimod has been shown to be useful as a vaccine adjuvant. It has also been shown to enhance T helper type 1 cytokine release while suppressing T helper type 2 cytokine production.

Although some of the beneficial effects of resiquimod are known, the discovery of additional therapeutic or prophylactic benefits of this compound via novel dosing regimens is ongoing. The present disclosure is directed to such discoveries.

Summary of the Invention

The invention is directed to dosing regimens effective for delaying the recurrence of clinical symptoms associated with a human herpes virus infection.

It will be noted that in several places throughout the specification, guidance is provided through lists of examples. In each instance, the recited list serves only as a representative group. It is not meant, however, that the list is exclusive.

In one embodiment, the invention provides a method for delaying recurrence of symptoms caused by a herpes virus infection. The method includes a step of administering a pharmaceutical formulation containing from about 0.001 percent to about 0.05 percent by weight of resiquimod, based on total weight of the formulation, to a herpes virus lesion. The formulation can be administered to the lesion and can be administered until the lesion is resolved, or for a period of time beyond resolution of the lesion. The formulation can be administered at least one time per week, typically at least two times per week or three times per week, and in some embodiments, daily or every other day. The invention is particularly advantageous for use in delaying recurrence of symptoms associated with HSV-1 or HSV-2. In some embodiments, recurrence of clinical symptoms can be delayed for at least 120 days after first administration of the pharmaceutical formulation, typically for at least 120 days after the completion of one treatment cycle.

In another embodiment, the invention provides a method for delaying recurrence of a herpes virus infection including a step of topically administering a pharmaceutical

formulation including 0.01 percent, based on total weight of the formulation, of resiquimod to a herpes virus lesion at least one time per week for at least one week.

Detailed Description

The present invention is directed to novel dosing regimens for delaying the recurrence of clinical symptoms associated with human herpes virus infection after resolution of prior clinical symptoms caused by the virus. As used herein, a "herpes virus" refers to members of the herpetoviridae family including herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV-6), human herpes virus 7 (HHV-7) and human herpes virus 8 (HHV-8). The invention is particularly advantageous for use to delay recrudescence of symptoms associated with HSV-1 and HSV-2.

Methods for preparing resiquimod are known and disclosed in, for example, U.S. Patent No. 5,389,640 (Gerster). Pharmaceutical formulations containing resiquimod and methods for preparing them are disclosed in U.S. Patent No. 5,939,090 (Beaurline). Other suitable formulations are known and can be used according to the invention including, for example, formulations disclosed in U.S. Patent 6,245,776 (Skwierczynski). The entire disclosure of each of these patents are incorporated herein by reference.

Clinical symptoms associated with herpes viruses are well known. Lesions typical for orolabial herpes include painful vesicular eruptions with distinct vesicles appearing on the lips, tongue, or buccal mucosa. The vesicles can quickly coalesce and rupture to form shallow ulcers covered with whitish yellow necrotic material. Clinical symptoms typical for genital herpes include small, grouped vesicles on erythematous bases. The vesicles can

unroof spontaneously or by direct abrasion to form, ulcerations. The ulcerations typically form a crust and then undergo re-epithelialization.

According to the invention, a pharmaceutical formulation containing resiquimod can be administered to the lesions when first apparent. The formulation may also be applied to the visible lesion site after resolution of the lesion. The pharmaceutical formulation can be topically applied to the lesions or lesion sites. The pharmaceutical formulation contains resiquimod in an amount about 0.001 to 0.05 percent by weight, preferably about 0.01 percent by weight, based on the total weight of the formulation.

The formulation can be administered to lesions at least one time per week (1X/week). Administration of the formulation is typically greater than one time per week (1X/week), more typically at least two times per week (2X/week) or three times per week (3X/week) and, in some embodiments, daily or every other day. Because treatment according to the invention is most easily administered to lesions, treatment typically commences once lesions are visible. Treatment according to the invention may be administered for a period of about 1 to 18 weeks, typically about 1 to 6 weeks, and preferably about 3 to 4 weeks. Generally about 125 mg ± 10% of gel per 10 cm^2 of treatment area or about 150 mg ± 10% of gel per 15 cm^2 of treatment area or about 225 mg ± 10% of gel per 20 cm^2 of treatment area is applied. The pharmaceutical formulation can remain on the lesions for about 6 to 12 hours, typically about 8 to 10 hours.

In some embodiments, when a formulation containing resiquimod was administered to a population of patients having herpetic lesions, after cessation of treatment, clinical symptoms did not recur for a median time of at least 120 days, typically at least 150 days, in some embodiments at least 172 days and in some embodiments at least 190 days.

Unlike other anti-herpetic compounds which inhibit recurrence of herpes virus while the drug is being administered, the regimens disclosed herein provide for inhibition of recurrence of herpes virus symptoms after cessation of resiquimod administration. While not wishing to be bound by a single theory, it is believed that the advantageous features of the present invention may be due to the coupling of the immune enhancing cytokines induced by resiquimod with the endogenous antigen which is present during the recurrence to provide enhanced cell mediated immunity.

EXAMPLES

The following Examples are provided to further describe the invention and should not be intended to limit the scope of the invention to the Examples.

Example 1

Preparation of resiquimod formulations

Propylene glycol (700 g) and resiquimod (4-amino-2-ethoxymethyl-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol, 1.4 g) were added to a 1000 mL glass beaker. The resulting mixture was heated (about 55° C.) with stirring until all of the resiquimod was dissolved. The resulting solution was added to the mixing bowl of a ROSS LDM-4 mixer. Triacetin (11,968.7 g) was added to the mixing bowl and the resulting mixture was mixed for 10 minutes at 36 rpm. Colloidal silicon dioxide (1,330.0 g, AEROSIL ® 200 from Degussa, Frankfurt, Germany) was added in five parts. After each addition the resulting mixture was mixed at ambient pressure for 1 to 2 minutes at 36 rpm and then under vacuum (18 inches of Hg below ambient pressure, about 4.0 x 10^5 Pa) for about 9 minutes at 36 rpm. The sides of the mixing bowl and the mixing blades were scraped. The formulation was mixed under vacuum (17 inches of Hg below ambient pressure, about 4.3

X 10^5 Pa) for about 10 minutes at 36 rpm. The resulting gel contained 0.01% resiquimod, 5.0% propylene glycol, 9.5% colloidal silicon dioxide, and 85.49% triacetin.

Using the method described above, a second formulation was prepared by combining 7.0 g of resiquimod, 700.0 g of propylene glycol, 11963.0 g of triacetin and 1,330.0 g of colloidal silicon dioxide. The resulting gel contained 0.05% resiquimod, 5.0% propylene glycol, 9.5% colloidal silicon dioxide, and 85.45% triacetin.

Clinical study of resiquimod formulations applied to herpetic patients

A randomized, double-blind vehicle (placebo)-controlled study was performed to evaluate single and multi-weekly doses of the resiquimod formulations prepared above topically applied to herpetic lesions on the skin of the external genitalia.

52 otherwise healthy patients (20 to 60 years of age, inclusive) with a history of recurrent herpes genitalis ($\geq$ 6 episodes per year) participated in the study. All patients had clinically inactive herpes genitalis two weeks before and at the time of screening for entry into the study. After passing screening, patients were enrolled into a 12-week eligibility period to qualify for treatment by virtue of experiencing a herpetic recurrence. During the eligibility period patients qualified for the treatment period by coming to the study site for treatment visit one within 24 hours of a recurrence. At this visit patients were stratified by sex and enrolled sequentially into an active treatment or vehicle treatment regimen.

The treatment period began with the first treatment visit and ended with the final treatment visit. The treatment groups were 0.05 percent resiquimod containing formulation or formulation alone (vehicle) 1X/week for 4 weeks; 0.05 percent resiquimod containing formulation or formulation alone 2X/week for 3 weeks; 0.01 percent

resiquimod formulation or formulation alone 2X/week for 3 weeks; or 0.01 percent resiquimod formulation or formulation alone 3X/week for 3 weeks.

Efficacy evaluations included assessment of time to recurrence in a 6 month observation period; total number of recurrences in the observation period; and the size, number and duration of lesions during recurrences in the observation period.

After the first visit, all patients returned the following day, and subsequently on their scheduled visits according to their dosing regimens, and 5 to 7 days after their last application of study formulation. The 6-month observation period began immediately after the treatment period, and patients returned to the clinic at 1, 3 and 6 months. During the observation period patients also returned to the clinic within 72 hours of each recurrence, and a clinic staff personnel verified and documented all herpetic lesions. The results of the study are shown in Table I below.

Table I

Resiquimod Concentration	Dosing Frequency	Duration of Treatment	Median No. Days to Recurrence after treatment cessation
0.05%	1x/wk	4 weeks	>60
0.05%	2x/wk	3 weeks	105
0.01%	2x/wk	3 weeks	172.5
0.01%	3x/wk	3 weeks	>195
Vehicle*			57

*Summary of the vehicle controls from the four treatment groups

Through this study, it was discovered that delay in recurrence of herpetic lesions was more prolonged using lower concentration resiquimod formulations than higher concentration formulations. The delay in recurrence is also associated with increasing frequency of administration rather than increasing concentration.

Example 2

Topical Application of IRM Formulation to Orolabial Herpetic Lesions

A pharmaceutical formulation containing .001 percent or .01 percent, by weight, based on total formulation weight, of resiquimod can be applied to orolabial lesions caused by a herpes virus. The pharmaceutical formulation can be topically applied to the lesions or lesion sites at least once per week for at least one a week using regimens and application methods as described herein.

From the foregoing detailed description and Examples, it will be evident that modifications and variations can be made in the products and processes of the invention without departing from the spirit or scope of the invention. Therefore, it is intended that all modifications and variations not departing from the spirit of the invention come within the scope of the claims and their equivalents.

WE CLAIM:

1. Use of 4-amino-α,α-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol for the manufacture of a pharmaceutical formulation for delaying recrudescence of a herpes virus infection after administration of the pharmaceutical formulation to a patient wherein the pharmaceutical formulation includes from 0.001 percent to 0.05 percent by weight, based on the total weight of the formulation, of 4-amino-α,α-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol and the formulation is administered to a herpes virus lesion at least one time per week for at least one week.

2. The use according to claim 1 wherein the 4-amino-α,α-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol is present in an amount of 0.01 percent to 0.05 percent by weight, based on total weight of the formulation.

3. The use according to claim 1 wherein the 4-amino-α,α-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol is present in an amount of 0.01 percent by weight, based on total weight of the formulation.

4. The use according to claim 1 wherein the herpes virus lesion is an anogenital lesion.

5. The use according to claim 1 wherein the herpes virus lesion is an orolabial lesion.

6. The use according to claim 1 wherein the pharmaceutical formulation is administered at least one time per week for at least 2 weeks.

7. The use according to claim 1 wherein the pharmaceutical formulation is administered at least one time per week for at least 3 weeks.

8. The use according to claim 1 wherein the herpes virus infection is caused by HSV-2.

9. The use according to claim 1 wherein the herpes virus infection is caused by HSV-1.

10. The use according to claim 1 wherein the pharmaceutical formulation is administered at least two times per week.

11. The use according to claim 10 wherein the pharmaceutical formulation is administered for at least two weeks.

12. The use according to claim 10 wherein the pharmaceutical formulation is administered for at least three weeks.

13. The use according to claim 1 wherein the pharmaceutical formulation is administered at least three times per week.

14. The use according to claim 13 wherein the pharmaceutical formulation is administered for at least two weeks.

15. The use according to claim 13 wherein the pharmaceutical formulation is administered for at least three weeks.

16 The use according to claim 1 wherein the pharmaceutical formulation is administered every other day.

17. The use according to claim 16 wherein the pharmaceutical formulation is administered for at least two weeks.

18. The use according to claim 16 wherein the pharmaceutical formulation is administered for at least three weeks.

19. The use according to claim 1 wherein the pharmaceutical formulation is administered daily.

20. The use according to claim 19 wherein the pharmaceutical formulation is administered for at least two weeks.

21. The use according to claim 19 wherein the pharmaceutical formulation is administered for at least three weeks.

22. Use of 4-amino-α,α-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol for the manufacture of a pharmaceutical formulation for delaying recrudescence of a herpes virus infection after administration of the pharmaceutical formulation to a patient wherein the pharmaceutical formulation includes 0.01 percent by weight, based on the total weight of the formulation, of 4-amino-α,α-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol and the formulation is administered to a herpes virus lesion at least until the lesion is resolved.

23. The use according to claim 22 wherein the pharmaceutical formulation is administered for a period of 1 to 4 weeks after the lesion is resolved.

24. The use according to claim 22 wherein the pharmaceutical formulation is administered to the lesion at least one time per week.

25. The use according to claim 22 wherein the pharmaceutical formulation is administered to the lesion at least two times per week.

26. The use according to claim 22 wherein the pharmaceutical formulation is administered to the lesion at least three times per week.

27. The use according to claim 22 wherein the herpes virus lesion is an anogenital lesion.

28. The use according to claim 22 wherein the herpes virus lesion is an orolabial lesion.

29. The use according to claim 22 wherein the pharmaceutical formulation is topically administered to the lesion.

30. The use according to claim 22 wherein the herpes virus is HSV-2.

31. The use according to claim 22 wherein the herpes virus is HSV-1.

32. The use according to claim 22 wherein recurrence of clinical symptoms is delayed for at least 120 days after first administration of the pharmaceutical formulation to the lesion.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 01/28764

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/47 A61P31/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 20847 A (MINNESOTA MINING & MFG) 28 October 1993 (1993-10-28) abstract	1-31
X	US 5 939 090 A (RODDY PATRICK J ET AL) 17 August 1999 (1999-08-17) cited in the application abstract	1-31
X	US 5 389 640 A (GERSTER JOHN F ET AL) 14 February 1995 (1995-02-14) cited in the application abstract	1-31
A	EP 0 823 426 A (HOFFMANN LA ROCHE) 11 February 1998 (1998-02-11) abstract claims 1-22	1-31

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 November 2001	13/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Taylor, G.M.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 01/28764

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 25030 A (SMITHKLINE BEECHAM CORP ;KINGSBURY WILLIAM DENNIS (US); PENDRAK IS) 10 November 1994 (1994-11-10) abstract claims 1-15	1-31
P,X	SPRUANCE, S.L.; TYRING, S.K.; SMITH, M.H.; MENG, T.C.: "Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: a pilot study" JOURNAL OF INFECTIOUS DISEASES, vol. 184, no. 2, 15 July 2001 (2001-07-15), pages 196-200, XP001037771 abstract	1-31

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 32

Present claim 32 relate to a product defined by reference to a desirable characteristic or property, namely that recurrence of clinical symptoms is delayed for at least 120 days after first administration of the pharmaceutical formulation to the lesion.

The claim lacks clarity (Art. 6 PCT). An attempt is made to define the product by reference to a result to be achieved. This lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, claim 32 has not been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/US 01/28764

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9320847 A	28-10-1993	AT 142110 T	15-09-1996
		AU 674313 B2	19-12-1996
		AU 4048093 A	18-11-1993
		DE 69304521 D1	10-10-1996
		DE 69304521 T2	20-02-1997
		DK 636031 T3	24-02-1997
		EP 0636031 A1	01-02-1995
		ES 2092306 T3	16-11-1996
		HK 1007962 A1	30-04-1999
		HU 69993 A2	28-09-1995
		HU 9500752 A3	28-11-1995
		IL 105325 A	14-11-1996
		JP 7505883 T	29-06-1995
		KR 263804 B1	16-08-2000
		MX 9302199 A1	31-08-1994
		NO 943920 A	14-10-1994
		NZ 252020 A	21-12-1995
		NZ 280098 A	26-06-1998
		WO 9320847 A1	28-10-1993
		US 6083505 A	04-07-2000
		ZA 9302627 A	14-10-1994
US 5939090 A	17-08-1999	AU 723897 B2	07-09-2000
		AU 5368698 A	29-06-1998
		BR 9713677 A	28-03-2000
		CZ 9901955 A3	15-09-1999
		EP 0942724 A2	22-09-1999
		HU 0000568 A2	28-10-2000
		JP 2001501968 T	13-02-2001
		NO 992638 A	16-07-1999
		WO 9824436 A2	11-06-1998
US 5389640 A	14-02-1995	US 5977366 A	02-11-1999
		US 5605899 A	25-02-1997
		US 5741909 A	21-04-1998
		AT 179711 T	15-05-1999
		AU 658621 B2	27-04-1995
		AU 1566992 A	06-10-1992
		AU 673309 B2	31-10-1996
		AU 2715795 A	21-09-1995
		CA 2104782 A1	02-09-1992
		CZ 9301788 A3	18-10-1995
		DE 69229114 D1	10-06-1999
		DE 69229114 T2	04-11-1999
		DK 582581 T3	08-11-1999
		EP 0582581 A1	16-02-1994
		EP 0872478 A2	21-10-1998
		ES 2131070 T3	16-07-1999
		HU 67026 A2	30-01-1995
		HU 211242 B3	28-11-1995
		IE 920605 A1	09-09-1992
		IL 101110 A	08-12-1995
		IL 114570 A	31-10-1996
		JP 2955019 B2	04-10-1999
		JP 6504789 T	02-06-1994
		KR 235389 B1	15-12-1999
		NO 933069 A	01-11-1993
		NZ 241784 A	27-06-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte nal Application No
PCT/US 01/28764

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5389640 A		SG 46492 A1	20-02-1998
		SG 70625 A1	22-02-2000
		WO 9215582 A1	17-09-1992
		ZA 9201540 A	25-11-1992
EP 0823426 A	11-02-1998	BR 9704271 A	03-11-1998
		CA 2210415 A1	07-02-1998
		EP 0823426 A1	11-02-1998
		JP 10067749 A	10-03-1998
		TR 9700761 A2	21-02-1998
		US 6162918 A	19-12-2000
		US 5969139 A	19-10-1999
WO 9425030 A	10-11-1994	WO 9425030 A1	10-11-1994